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13. ABSTRACT ***(Maximum 200 Words)***

The purpose of this research is to develop a rodent prostate cancer model and to investigate the potential of genistein to suppress the development of this cancer. We have hypothesized that exposure to genistein, a component of soy, during early critical periods of development will modulate development of hormone responsive target organs and cell differentiation. We further hypothesized that these developmental modifications set the program for later response to hormonally-active effectors. We believe that programming events play a significant role in determining susceptibility for prostate cancer. Starting at conception, rats were exposed to 0, 25- and 250 mg genistein/kg AIN-76A diet. Seven week old male offspring were injected orthotopically into the dorsolateral prostate with the carcinogen, N-methylnitrosurea (NMU), for the induction of adenocarcinomas which takes 12 months. Animals are being palpated on a weekly basis for tumors (to be continued in the second year). Also, we have measured, in 187 day old rats exposed ± genistein and to NMU, biomarkers in the dorsolateral prostate. mRNA and protein levels of EGF-receptor and androgen receptor were not altered.Understanding the in vivo mechanism of genistein action should allow soy, genistein, or potent genistein analogues to be used against prostate cancer in humans.

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FOREWORD

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N/A For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

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N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

C.A. Lamartiniere 8/26/99

PI - Signature Date

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Introduction

The purpose of this research is to develop a rodent prostate cancer model and to investigate the potential of genistein to suppress the development of this cancer. We have hypothesized that exposure to genistein, a component of soy, during early critical periods of development would modulate development of hormone responsive target organs and cell differentiation. We further hypothesized that these developmental modifications set the program for later response to hormonally-active effectors. We believe that programming events play a significant role in determining susceptibility for prostate cancer. Our specific aims are: 1) to investigate the potential of life-time exposure (including perinatal) to genistein in the diet to imprint for reduced susceptibility for prostate cancer, 2) to determine if life-time exposure to genistein in the diet will down-regulate EGF receptor levels in prostates of adult rats and 3) to determine the concentrations of genistein and its metabolites in blood and dorsolateral prostates of male offspring fed genistein in the diet. Understanding the in vivo mechanism of genistein action will allow soy, genistein, or potent genistein analogues to be used against prostate cancer in humans.

Body

Task 1) To determine if life-time genistein in the diet protects against chemically-induced prostate cancer (years 1 and 2). Virgin female Sprague Dawley-CD rats were purchased and fed either 0, 25 mg, or 250 mg genistein/kg AIN-76A diet from 2 weeks prior to initiation of breeding, until offspring are killed. At 70 days postpartum, the carcinogen, MNU, was injected into the prostate. These animals continue to be palpated for prostate tumors. It takes 12 months for the tumors to develop.

This specific aim has been complicated by the aggressive behavior of these animals, resulting in having to house these rats 1/cage. Hence, the cost of animal housing has escalated (3x).

Task 2) From the dorsolateral prostates of rats exposed ± genistein we will investigate the expression of the EGF-receptor (year 1). In 117 day old rats exposed to NMU, ± genistein, no difference in mRNA and protein levels of EGF-receptor and androgen receptor was found. We will also measure mRNa levels of estrogen receptors-alpha and beta.

Task 3) To determine the concentrations of genistein and its metabolites in blood and dorsolateral prostates of male offspring fed genistein in the diet. Feed consumption and isoflavone content of the diets will be determined. This will provide data on bioavailability. Identification and quantitation will be done by H.P.L.C.-mass spectrometry. This will be done in the second year.

Key Research Accomplishments

The NMU rat prostate cancer model has been initiated and two groups on genistein have been set up to investigate chemoprevention. Life-time exposure to genistein does not alter mRNA and protein levels of EGF-receptor and androgen receptor.

Reportable Outcomes/Conclusions

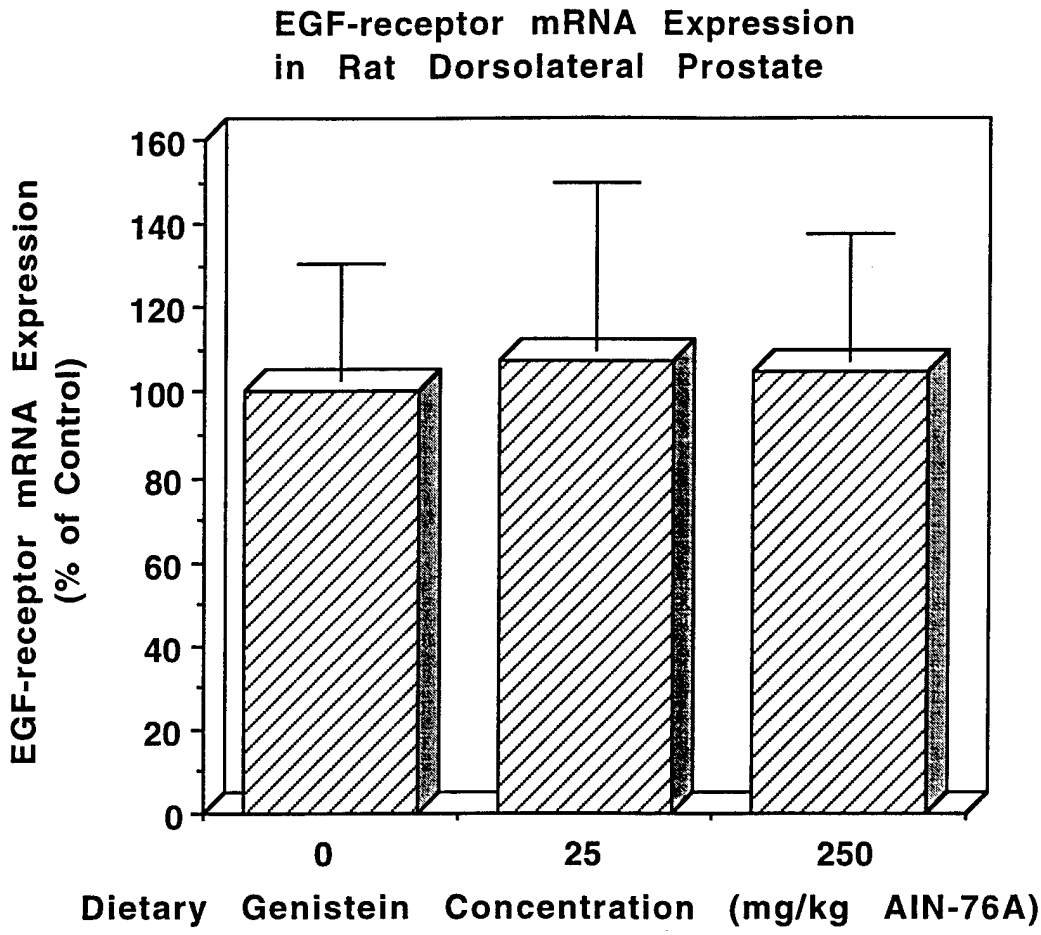
In this model system dietary genistein does not modulate the EGF-receptor or the androgen receptor. Since the tumor study is a development study, we do not yet have any significant reportable outcomes or conclusions.

References

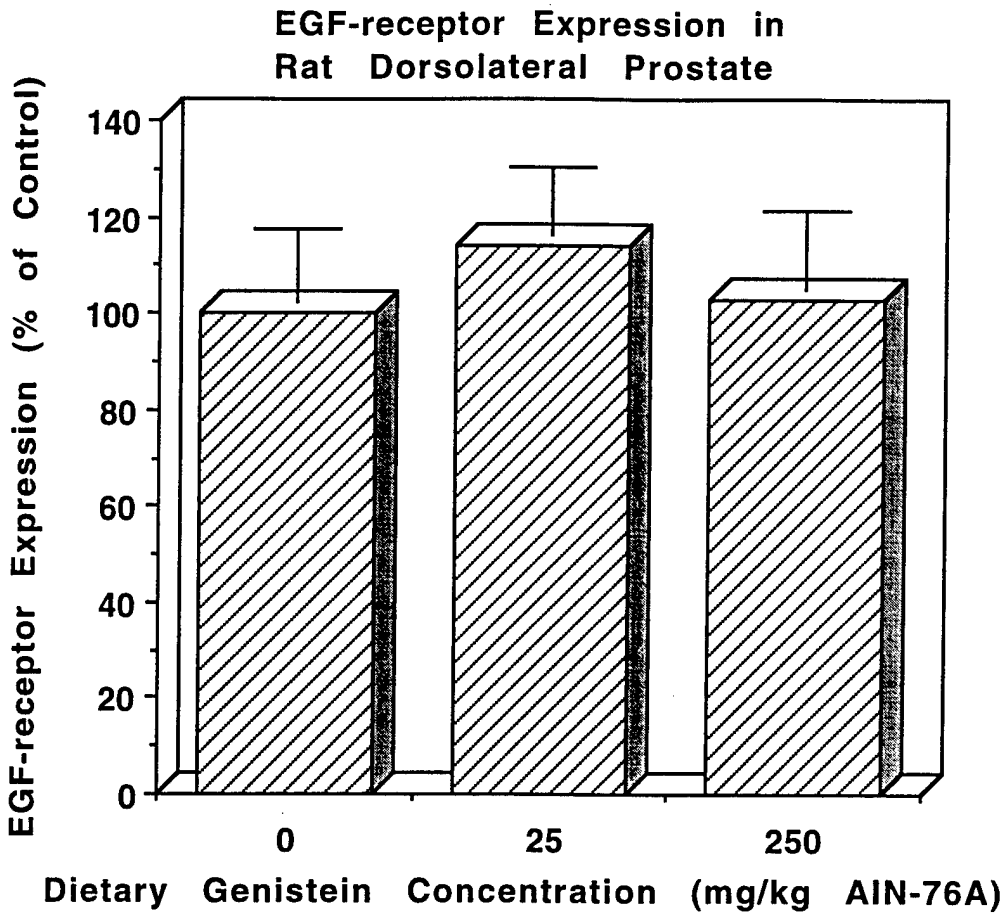
Not applicable.

Appendices

Four Figures



EGF-receptor mRNA levels in dorsolateral prostates of Lobund-Wistar rats fed genistein in the diet from conception through day 187. At day 70 postpartum, all rats were injected with 42 mg N-methylnitrosourea/kg body weight into the dorsolateral prostate. All animals received silastic implants of testosterone (2 cm x 0.2 cm) every 12 weeks. Rats received either zero, 25 mg genistein, or 250 mg genistein/kg AIN-76A diet. RNA from the dorsolateral prostate was isolated, reverse transcribed and amplified. PCR products for the EGF-receptor were verified by Southern blots with oligonucleotide probes. Detection of fluorescent signal was analyzed by densitometry. The data have been expressed as a percentage of mRNA level of the controls. Each group contained 6 samples, each from different rats. No statistical significance was detected between treated groups and controls.



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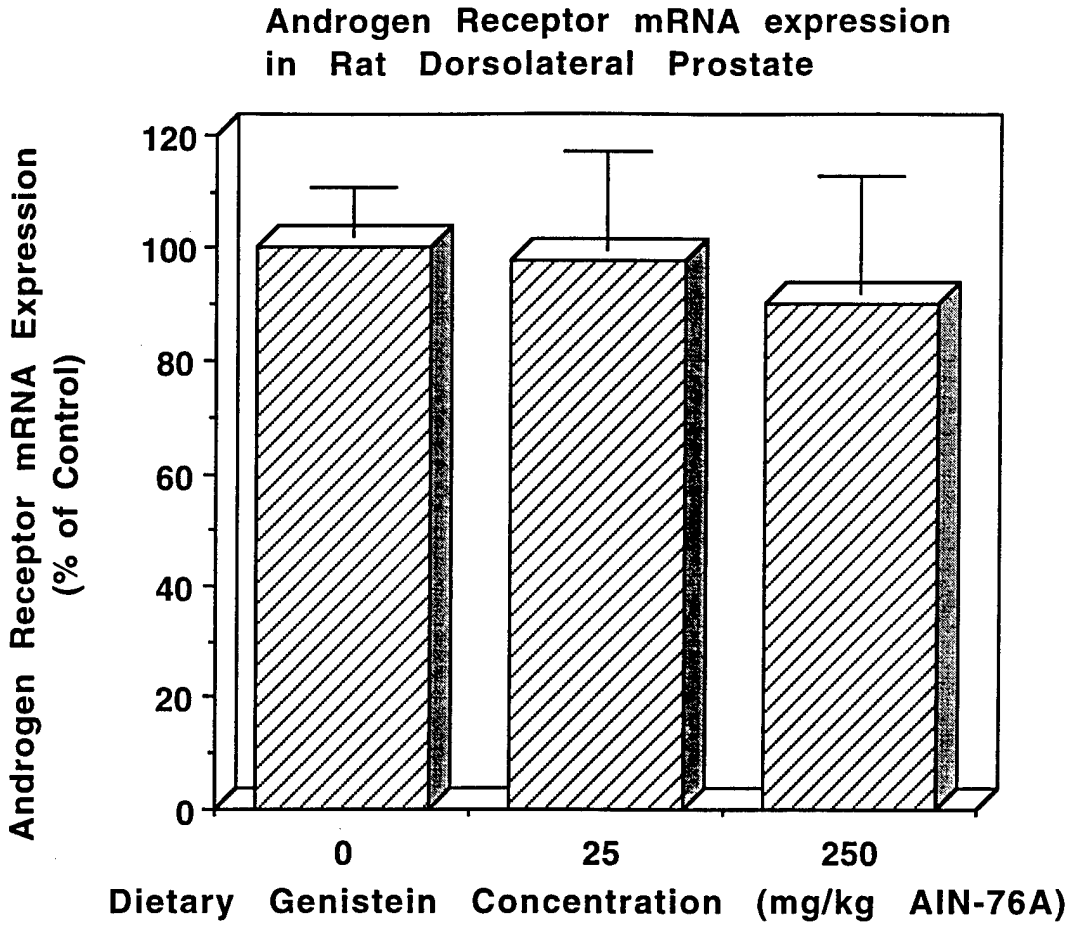
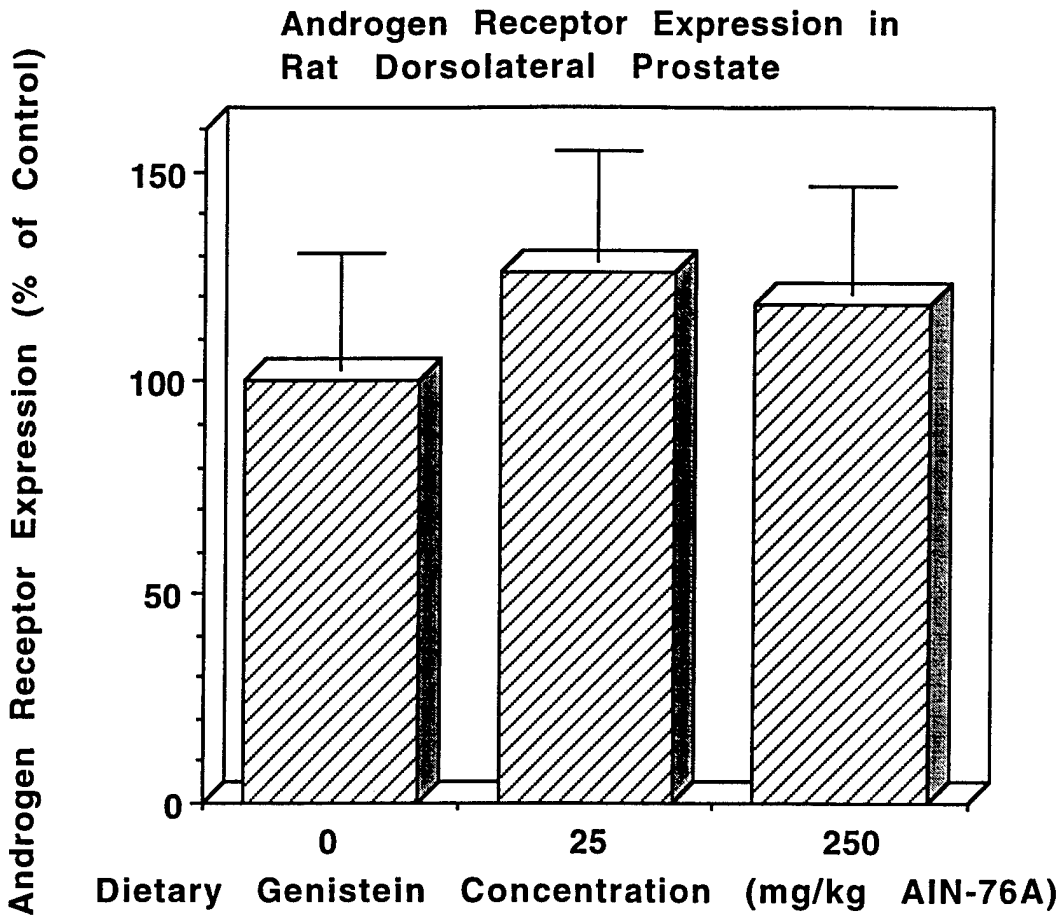


Androgen receptor mRNA levels in dorsolateral prostates of Lobund-Wistar rats fed genistein in the diet from conception through day 187. At day 70 postpartum, all rats were injected with 42 mg N-methylnitrosourea/kg body weight into the dorsolateral prostate. All animals received silastic implants of testosterone (2 cm x 0.2 cm) every 12 weeks. Rats received either zero, 25 mg genistein, or 250 mg genistein/kg AIN-76A diet. RNA from dorsolateral prostate was isolated, reverse transcribed and amplified. PCR products for the androgen receptor were verified by Southern blots with oligonucleotide probes. Detection of fluorescent signal was analyzed by densitometry. The data have been expressed as a percentage of mRNA level of the controls. Each group contained 6 samples, each from different rats. No statistical significance was detected between treated groups and controls.



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